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A Novel *TAZ* Gene Mutation and Mosaicism in a Polish Family with Barth Syndrome

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Summary

Barth syndrome (BTHS) is an X-linked recessive disease primarily affecting males. Clinically, the disease is characterized by hypertrophic or dilated cardiomyopathy, skeletal myopathy, chronic/cyclic neutropenia, 3-methylglutaconic aciduria, growth retardation and respiratory chain dysfunction. It is caused by mutations in the *TAZ* gene coding for the tafazzin protein which is responsible for cardiolipin remodeling. In this work, we present a novel pathogenic *TAZ* mutation c.83T>A, p.Val28Glu, found in mosaic form in almost all female members of a Polish family. Sanger sequencing of DNA from peripheral blood and from epithelial cells showed female mosaicism in three generations. This appears to be a new mechanism of inheritance and further research is required in order to understand the mechanism of this mosaicism. We conclude that BTHS genetic testing should include two or more tissues for women that appear to be noncarriers when blood DNA is initially tested. The results of our study should not only be applicable to BTHS families, but also to families with other X-linked diseases.

Keywords: Barth Syndrome, cardiomyopathy, *TAZ* gene, tafazzin, inherited mosaicism

Introduction

Barth syndrome (BTHS, OMIM 302060) is a rare lipid metabolism disorder first described in 1983 by Barth et al. (Barth et al., 1983; Bione et al., 1996). It is an X-linked recessive inherited disease. Typically, it is characterized by hypertrophic or dilated cardiomyopathy (CMP), skeletal myopathy, chronic or cyclic neutropenia, 3-methylglutaconic aciduria, as well as growth retardation and respiratory chain dysfunction (Chitayat et al., 1992; Christodoulou et al., 1994; Besley et al., 1995; Barth et al., 2004; Spencer et al., 2006). Incidence of BTHS has been estimated as 1 in 300,000–400,000 in the United States and 1 in 140,000 in the United Kingdom, although more accurate incidence is not known and it seems to be an underdiagnosed condition (Barth Syndrome Foundation: http://www.barthsyndrome.org/home; Clarke et al., 2013). Laboratory testing to confirm the clinical diagnosis is based on urinary 3-methylglutaconic acid (3-MGCA) testing, monolysocardiolipin/cardiolipin(MLCL:L4-CL) ratio testing and tafazzin gene (*TAZ,* previously termed *G4.5*) sequencing (especially when CL testing is not available; Clarke et al., 2013).

BTHS is caused by various mutations in the *TAZ* gene, located in region Xq28; it contains 11 short exons and 10 introns (Barth et al., 1983; Bolhuis et al., 1991; Bione et al., 1996; Gonzalez, 2005; Spencer et al., 2006; Aradhya et al., 2012). This 10,966 base pair-long gene encodes taffazin – phospholipid-lysophospholipid transacylase protein with phospholipid acyltransferase function. Taffazin plays an important role in remodeling of CL and phosphatidylglycerol structure (Barth et al., 1983).

CL is a component of the inner mitochondrial membrane and is involved in the mitochondrial electron transport chain (Raja & Greenberg, 2014), playing an essential role in cellular energy metabolism, mitochondrial dynamics and the inception of apoptotic pathways (Raja & Greenberg, 2014). It was demonstrated that the loss of CL in the inner mitochondrial membrane results in respiratory chain dysfunction, most specifically of complexes I, III and IV (Barth et al., 2004; Brandner et al., 2005; McKenzie et al., 2006). To date, more than 150 different *TAZ* gene mutations have been identified

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in patients with diagnosed BTHS [Human Tafazzin (*TAZ*) Gene Mutation and Variation Database, last updated August 18, 2014].

In this paper, we report a novel mutation in exon 1 of the *TAZ* gene and female mosaicism in three generations of a Polish family with BTHS.

Materials and Methods

Patient Report

Proband case report

The boy was the second child of a mother with family history of genetically inherited CMP. At 4 months of age, the proband was admitted to hospital due to heart failure signs: diarrhea preceded by feeding difficulties, cardiovascular instability, dyspnea, poor peripheral perfusion and neutropenia. On physical examination, loud systolic murmur in the whole precordium was found. Echocardiographic evaluation showed dilated CMP with EF 30%. Subsequently, the child experienced septic shock after staphylococcal infection. Cardiac function did not normalize and the patient presented numerous episodes of severe acute heart failure. Consequently, an inborn error of metabolism and genetic testing were considered. Biochemical investigations based on gas chromatography–mass spectrometry showed the absence of 3-methylglutaconic aciduria and presence of a small amount of p-hydroxyphenyllactic acid and p-hydroxyphenylpyruvic acid in urine. Blood samples were collected to perform genetic testing. The boy suddenly died at the age of 6 months.

The mother's family history led to suspicion of inherited CMP, specifically BTHS, based on two males: the 10-year-old son of the proband's aunt (IV-3) had CMP and has had a cardiac transplantation. In addition, a cousin's brother died suddenly at 3 weeks (IV-6).

In order to confirm the speculated clinical diagnosis of the proband, his parents, sister and grandmother were included in a molecular genetics study. Additional molecular analysis of the proband's male and female cousins, the mother`s cousins and their grandmother was performed. A detailed pedigree of the family was constructed (Fig. 1).

Molecular Genetic Studies

Total genomic DNA was isolated from peripheral blood cells and from buccal swab epithelial cells. Isolation was performed with High Pure PCR Template Preparation Kit (ROCHE Diagnostic, Mannheim, Germany). Sequences of primers specific to the *TAZ* gene were according to Johnston et al. and Vessel et al., as previously described (Johnston et al., 1997; Vesel et al., 2003). The 11 *TAZ* coding exons and adjacent intronic regions were amplified by PCR with FastStart PCR Master Kit (ROCHE Diagnostic). The sequences were determined on both DNA strands from at least two independent PCR products. The PCR products were purified with High Pure PCR Product Purification Kit (ROCHE Diagnostic) and sequenced with BigDye Terminator v.3.1 Cycle Sequencing Kit (Life Technologies, Foster City, CA, USA). The products of cycle sequencing were purified of unbound fluorescent dyes with BigDye XTerminator Purification Kit (Life Technologies, Foster City, CA, USA) and separated on the 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The sequences were analyzed by using AB DNA Sequencing Analysis Software v.5.2. (Applied Biosystems) and then were compared to the *TAZ* gene reference (NCBI GeneBank Reference Sequence Accession Numbers: NM_000116.3 and ENSEMBL database Accession Numbers: ENST00000299328).

Ethics statement

Informed consent was obtained from all family members.

Results

Mutation Analysis

A hemizygous c.83T>A substitution in *TAZ* exon 1 was found in peripheral blood DNA of the proband (IV-1). The mutation is predicted to result in the replacement of valine with glutamic acid (p.Val28Glu) in tafazzin. The mutation was not detected in the mother's (III-1) peripheral blood cell DNA, but was found in heterozygous form in DNA extracted from epithelial cells.

The maternal grandmother (II-1) of the patient is heterozygous for c.83T>A in peripheral blood cell DNA and in epithelial cell DNA. In the proband's sister (IV-2), the mutation was present neither in the peripheral blood nor in DNA from epithelial cells.

The proband's cousin (IV-3), who is affected with CMP, also carries the hemizygous mutation c.83T>A in both blood and epithelial cell DNA. Blood cell DNA from the mother (III-2) of this boy shows only traces of heterozygosity for the c.83T>A mutation, perhaps indicating a percentage of mosaicism in that tissue; DNA from her epithelial cells is clearly heterozygous at c.83. The boy's grandmother (II-2) is heterozygous for c.83T>A in epithelial but not in blood cells.

With regard to other family members, the proband's aunt (III-3, cousin of his mother) is heterozygous for c.83T>A only in DNA from epithelial cells, and her daughters (IV-5 and IV-6) also show heterozygosity in epithelial cells, but not in peripheral blood DNA. Heterozygosity for c.83T>A was also observed in the maternal grandmother (II-2).

Family pedigree is shown in Figure 2.

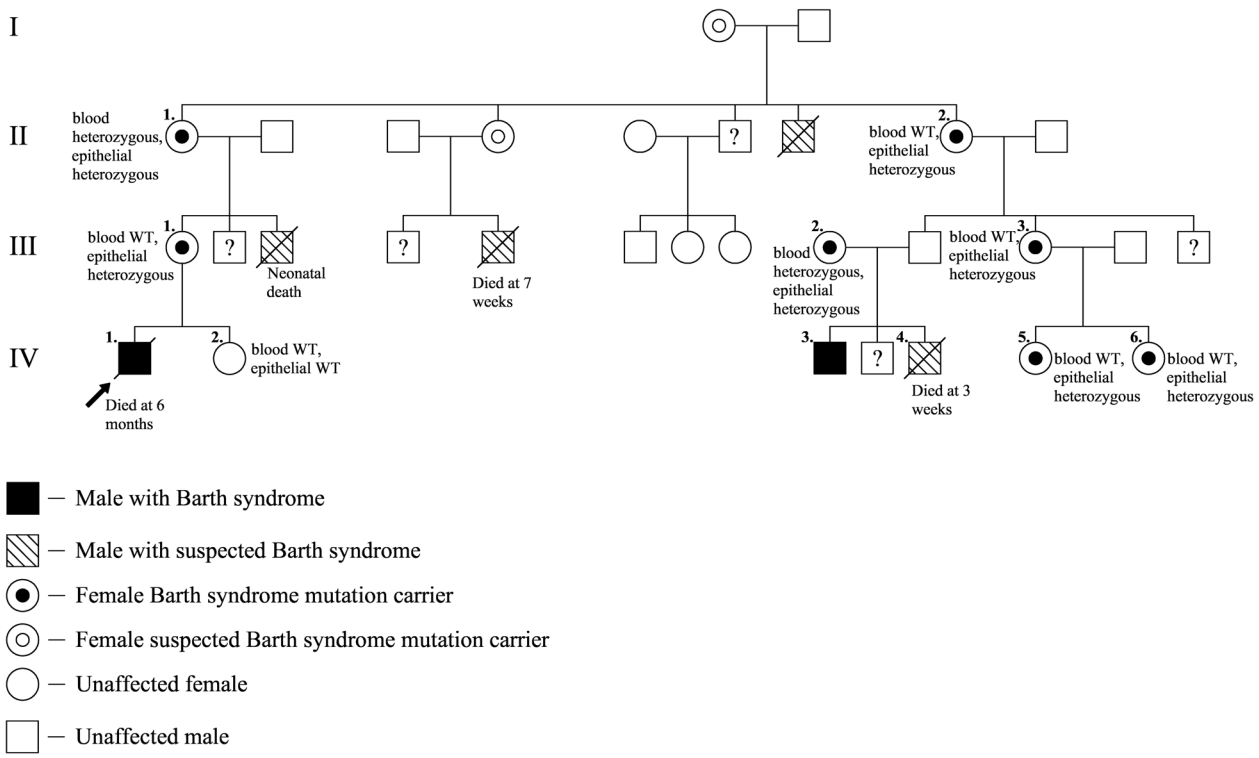

Figure 1 The pedigree of the family. The proband is indicated by the black arrow. Symbol with question mark "?" indicates an individual who did not have clinical evaluation and genetic testing. The blood and epithelial mutation status is described for each female carrier.

Discussion

We have found the novel exon 1 *TAZ* substitution c.83T>A (p.Val28Glu) in 10 members belonging to three generations of a Polish family.

This mutation has not been previously reported in the Human *TAZ* Gene Mutation and Variation Database (latest update August, 2014; http://www.barthsyndrome.org/home). A deletion of the entire codon (c. 82_84delGTG) is the only variant reported in this database for position Valine 28. In order to confirm whether the detected missense variant affects protein function, analysis using two programs, Sorting Intolerant From Tolerant (SIFT; http://sift.bii.a-star.edu.sg/www/SIFT_intersect_coding_submit.html) and Polymorphism Phenotyping v2 (PolyPhen-2; http://genetics.bwh.harvard.edu/pph2/) was conducted. This analysis supported the deleterious character of this mutation showing the PROVEAN score -5,670 (http://sift.bii.a-star.edu.sg/www/SIFT_intersect_coding_submit.html). Additionally, it was confirmed that the identified *TAZ* gene mutation occurs in the first exon, which is highly conserved between species (Landau et al., 2005). The position of 28Val in tafazzin shows a high degree of conservation in vertebrates and in arthropod invertebrates (Fig. 3; NCBI HomoloGene: https://www.ncbi.nlm.nih.gov/homologene; Edgar, 2004). Amino acid sequence conservation is very high for tafazzin. Comparison of the human tafazzin sequence to *Macaca mulatta* shows 98.5% conservation, 91.5% conservation compared to *Canis lupus familiaris,* 97.3% compared to *Bos Taurus,* 97.3% and 96.9%, respectively, to *Mus musculus* and *Rattus norvegicus* (NCBI HomoloGene: https://www.ncbi.nlm.nih.gov/homologene). Mutations which occur at positions that are conserved throughout evolution are more likely to be disease-causing (Ng & Henikoff, 2006). Analysis with the Alternative Splice Site Prediction (ASSP) program showed a loss of constitutive donor splice site in the presence of mutation c.83 T>A suggesting that this disruption of constitutive splicing may results in loss of gene expression (Faustino & Cooper, 2003). This hypothesis could be confirmed by testing the mRNA of affected male (IV-3) to see if it is mis-spliced.

Our proband as well as his male cousin affected with CMP manifested a wide range of clinical features typically associated with BTHS and originally described by Barth et al. (1983), which confirms that this newly discovered mutation p.Val28Glu is a mutation strongly affecting the normal function of the Taffazin protein and thus is pathogenic.

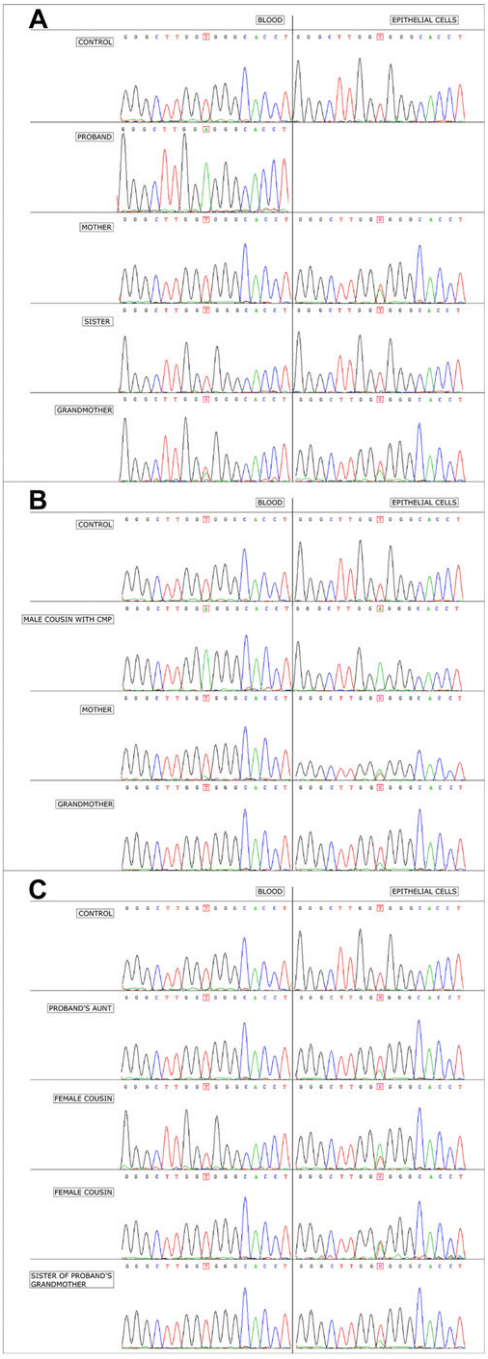

Figure 2 *TAZ* sequencing electropherograms showing position 83 of the coding DNA sequence (indicated by the red frame). (A) The results in the proband, his mother, sister and maternal grandmother. (B) The *TAZ* gene sequences of proband's cousins with CMP, his mother and maternal grandmother. (C) Results in other family members: proband's aunt, her two daughters and their maternal grandmother.

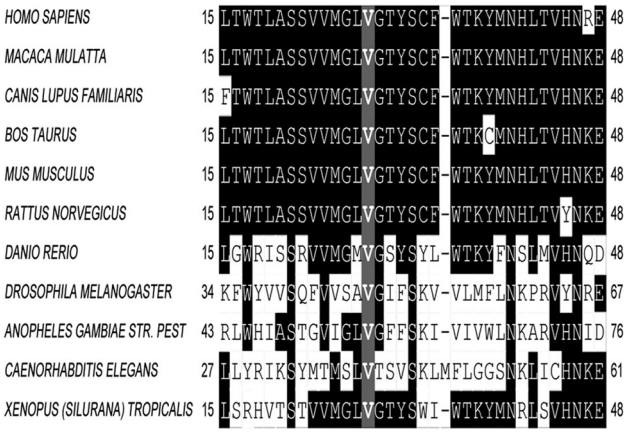

Figure 3 Multiple sequence alignment of the *TAZ* protein. We show the fragment of tafazzin between amino acids 15 and 48 in *homosapiens* and in other species. Alignment was generated by MUSCLE version 3.6. A Valine at amino acid position 28 is highlighted in gray. Identical amino acids are highlighted in black.

Tafazzin, the BTHS gene, encodes a MLCL transacylase that is the major contributor to the final acyl chain composition of mature CL (Bione et al., 1996; Xu et al., 2006). The process of CL acyl chain remodeling involves three distinct pathways, one of which is specifically affected in patients affected by Barth syndrome (Schlame & Ren, 2006). The importance of Valine at position 28 of tafazzin is supported by the CL deficiency observed in the individual with the p.Val28del mutation reported in the database.

Family studies showed that the proband's mother, maternal grandmother and aunt, as well as the male and female cousins, carry the same mutation. In addition, our analysis revealed somatic or both somatic and germline mosaicism in this family. Genetic mosaics are organisms having two or more genetically distinct populations of cells resulting from fertilization of one egg (Strachan & Read, 1999). Mosaicism can be tissue-specific or tissue-limited (Biesecker & Spinner, 2013) which is why we performed genetic testing of two different somatic tissues (mesoderm-derived lymphocytes and ectoderm-derived buccal epithelial cells). At the moment, there is only one scientific report on the occurrence of mosaicism in Barth syndrome (Chang et al., 2010) but many on the presence of different mosaicism types in other genetic diseases coupled with the X or autosomal chromosomes have been reported (Bakker et al., 1987; Puck et al., 1995; Forissier et al., 2000; Barbosa et al., 2008; Chiang et al., 2009; Alsina et al., 2013; Borgulová et al., 2013; Dufendach et al., 2013). In this family, it was found that the mutation p.Val28Glu is present in ectodermal as well as in mesodermal cells in the proband's grandmother and male cousin, whereas in samples taken from the proband's mother and aunts the mutation is

present only in mesodermal peripheral blood cells or at a low level of mosaicism in ectodermal buccal epithelial cells. The proband's female cousins carry the same mutation and distribution of mosaicism between epithelial cells and blood. On the basis of this study, occurrence of gonosomal (gonadal and somatic) mosaicism might be suspected. Confirmation of the prevalence of gonadal mosaicism in women is impossible because the germline DNA is not accessible (we cannot obtain oocytes for research; furthermore, every egg would have to be tested). Because the father did not transmit an X chromosome to his son, each mother must carry the *TAZ* mutation in her germline. For this reason, only germline mosaicism would be expected, although it could not be confirmed, and the transmission rate for future pregnancies is not known. This mutation has been passed through three generations attesting to the fact that at least part of the germline carries the mutation. We do not know if the germline is fully or partially affected.

We suppose that the mosaicism prevalent in the family could be inherited because it is present in different proportions in three generations of women carriers of the genetic disease. Genetic mosaics can result from mutations in the DNA, different epigenetic mechanisms, chromosomal aberrations and spontaneous reversion of inherited mutations (Youssoufian & Pyeritz, 2002). Further investigations, especially of the epigenetic processes which control cell fate, as well as parental imprinting and X chromosome inactivation, are needed. A mutation may arise in stem cells, during differentiation and in terminally differentiated somatic cells (Lupski, 2013). Coexistence of gonadal and somatic mosaicism in one person is possible when the mutation occurs during early embryogenesis before differentiation to germ layers (Youssoufian & Pyeritz, 2002). According to Zlotogora, if a germline mutation occurs before meiosis, it should be present in up to 50% of the gonadal cells (Zlotogora, 1998). Gonads can be fully affected with mutations when they have developed from a single mutant cell or can be partially affected if more precursor cells are involved in gonadal differentiation (van Essen et al., 2003). When the mosaicism is present in buccal epithelial cells, this may indicate that the mutation is also present in the cells derived from the ectodermal germ layer and arose only in this germ layer but not in others (Frederiksen and Andersen, 2006). The fact that a degree of mosaicism is also present in the blood of the proband's grandmother and aunt (II-1, III-2) may suggest that the mutation occurred before the division of the three germ layers. If a mutation has been transferred from the oocyte, all cells should have the mutation. In this family, almost all carriers of the mutation (excluding proband's grandmother (II-1), proband's aunt (III-2) and male cousin (IV-3)) do not have the mutated cells in the blood. Mosaicism in the somatic and/or gonadal tissues must originate at an early stage of zygote divisions, when mutations may arise *de novo*. In this case, it seems to be difficult to explain the mechanism of formation of the mutation which is inherited between three generations of the family. In our family, only DNA material from two tissues has been tested, therefore it is not known whether mosaicism also occurs in other tissues.

If an individual inherits a heterozygous mutation, present in all somatic cells, loss of the mutation would be possible due to a reversion mutation. Such a phenomenon might account for the loss of the mutation in some blood cells of the female carriers of the pedigree. However, this is an unlikely scenario as one nucleotide in three billion would have to be targeted in multiple individuals. An alternative would be loss of the X chromosome carrying the mutation in the cells (making them 45XO).

To summarize, we have presented an unusual family with three generations of female carriers who are mosaic for a mutation in the X-linked *TAZ* gene. This highlights a diagnostic testing problem for potential carriers who have an affected son: if she appears to be a noncarrier in her blood-derived DNA, she may still be a carrier in other tissues including the gonads. Follow-up testing should then be performed on buccal epithelial cells or on hair follicle DNA, the most easily accessible other tissues. For this family, genetic counseling is difficult in the absence of an estimated transmission risk.

Conflict of Interest Disclosures

The authors report no financial or other conflict of interest relevant to the subject of this article.

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